Vaccinia Gangrenosa

A Case in a Child with Hypogammaglobulinemia

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DESPITE the universal employment of Jennerian vaccination in the United States, serious complications are rare. Ordinary complications—febrile reactions, secondary bacterial infection of the vaccination site and nonspecific skin rashes—are self-limited. Postvaccinal encephalitis and generalized vaccinia are the most common of the severe complications.

The incidence of vaccination reactions has been variously reported from one in ten thousand to one in a million vaccinations.[7] Generalized vaccinia may occur in patients with healthy, intact skin as well as in those with preexisting skin lesions such as eczema or seborrhea. When the skin is normal, the course is self-limited and healing occurs as neutralizing antibodies appear. The dangers of vaccination in the presence of eczema are well recognized, the viremia which may follow primary vaccination favors dissemination. In addition, autoinoculation is an important factor in production of new lesions.

In a small number of cases the primary lesion does not heal, and additional similar lesions appear, then ulcerate and become secondarily infected. The mortality rate in such circumstances is extremely high. Recent evidence suggests that failure to produce a proper quantity or quality of virus neutralizing antibodies predisposes to generalized vaccinia of that type.[8] In some patients circulating gamma globulin is very low or absent, suggestive of inadequate antibody production. In others, gamma globulin production, although quantitatively sufficient, may be immunologically defective, so that effective neutralizing antibodies are not produced.

The following case is typical of generalized vaccinia gangrenosa with quantitatively deficient gamma globulin and inability to produce vaccinia virus neutralizing antibodies.

REPORT OF A CASE

The patient was a white infant boy, nine months of age. He had been born by normal delivery. The parents were healthy young adults. Two siblings had died at ages of four months and four days, respectively, of "infectious diarrhea" and "mongolism." Both the parents were successfully vaccinated as infants, but this had not been done in either sibling.

The patient was breast-fed for seven days after birth, and then weaned to a standard evaporated milk formula. When he was five months of age the formula was changed to soybean milk because of "allergy."

On October 21, 1955, at the age of seven months, the patient was vaccinated in the left deltoid region by the multiple pressure method. A week later a vesicular lesion was visible at the vaccination site and at 14 days the primary lesion had become encircled by many tiny vesicles. The day following the appearance of satellite lesions, larger and rapidly enlarging vesicles appeared on the palms and soles. On the 21st postvaccinal day, fever appeared and persisted until the day of hospital admission. Simultaneously, new vesicular lesions appeared on the hands, buttocks and neck. Treatment during this period consisted of local cleansing of the skin lesions and the administration of 5 cc. of gamma globulin intramuscularly.

The patient was admitted to the Los Angeles Children's Hospital, December 2, 1955.

Upon examination, multiple skin lesions of two types were noted. On the left deltoid region at the vaccination site was an ulcerated area of 4 cm. diameter. There were similar smaller lesions on the face, right arm and trunk. The remaining lesions, ranging from 3 to 6 mm. in diameter, were vesicular and were scattered over the arms and trunk. The hands and feet were covered by large bullae and denuded areas. Small ulcers were observed on the right side of the tongue and the soft palate.

Cultures of material from skin lesions, blood and stools consistently grew Pseudomonas and coagulase-positive hemolytic staphylococcus aureus. Repeated sensitivity studies were used to guide antibiotic therapy, as indicated in Chart 1.

Throughout the hospital stay there was moderately severe anemia requiring repeated blood transfusions to maintain the hemoglobin at 11 gm. per 100 cc. The number of leukocytes ranged from 6,000 to 12,000 per cu. mm. and there was a persistent pronounced shift to the left in the cell differential. The condition of the patient deteriorated steadily and he died 41 days after admittance. Despite large doses of gamma globulin, of hyperimmune vaccinal gamma globulin and of hyperimmune

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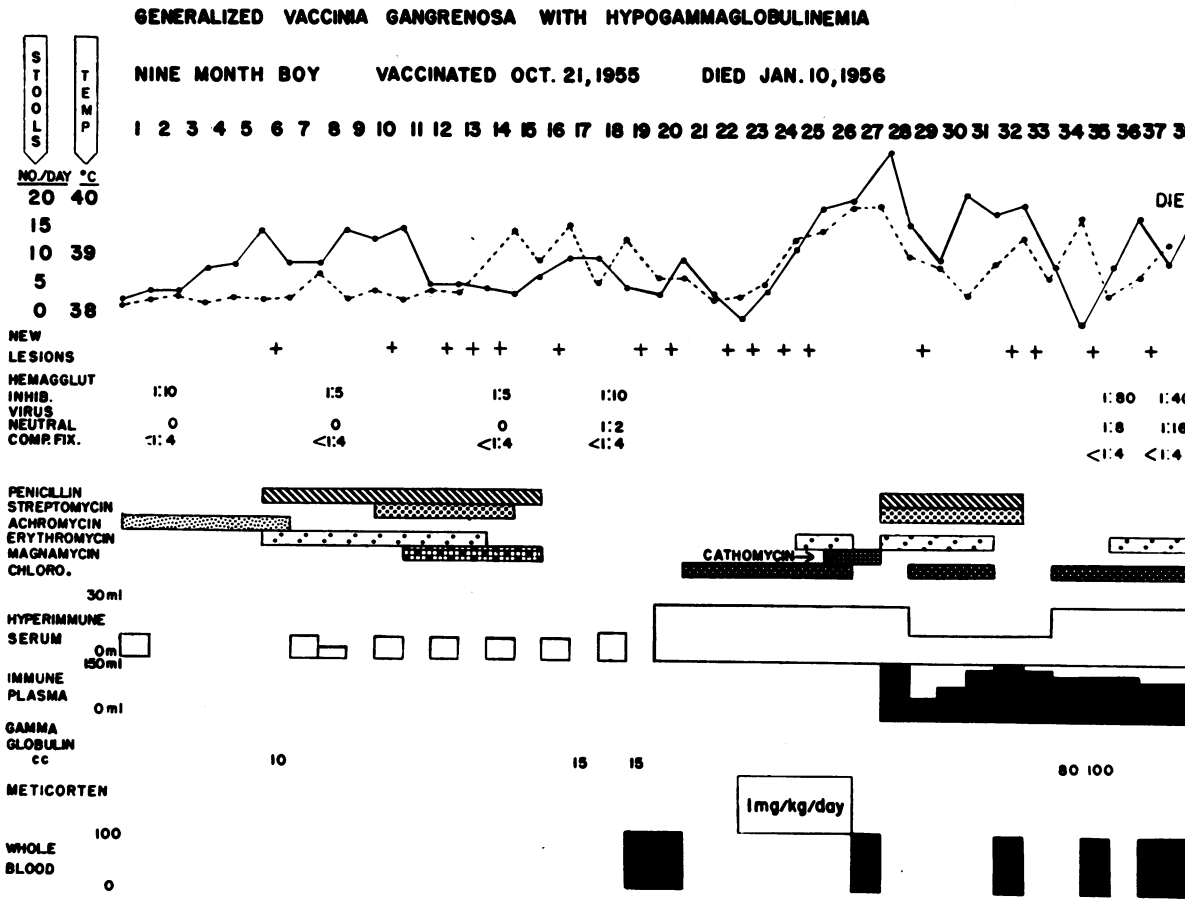

Chart 1.—Summary of clinical data and therapy during period of hospitalization.

vaccinia antiserum, new lesions continued to appear on the face, trunk and extremities. Existing lesions increased in size, some coalescing to form large expanding ulcers. On the seventh hospital day, fine tremors of the hands were first noted and generalized convulsions followed. Lumbar puncture was carried out and no spinal fluid abnormality was noted. On the tenth hospital day feedings were refused. Vomiting and diarrhea soon developed, and serious problems in the regulation of fluids, electrolytes and nutrition ensued.

Appropriate antibiotic therapy was administered in an effort to control secondary bacterial infection. All therapeutic efforts to modify the course of the disease failed.

SPECIAL STUDIES

I. Serum Protein Studies

Filter paper electrophoretic studies of the serum proteins were carried out with the Spinco Model R apparatus. Following migration, the proteins were heat-coagulated, stained with bromophenol blue, and fixed with sodium acetate. A Spinco Analytrol, a servo-type integrating scanner, was used to measure relative concentrations of protein fractions as indicated by amounts of dye present along the strips.

It is important to point out that the normal values tabulated in Table 1 are not entirely comparable to the patient's age group. Infant values were derived from cord blood of newborns. The abnormally low gamma globulin content on December 7, 1955 despite the administration of 15 cc. of gamma globulin in the preceding two weeks is significant. (This should account for a good portion of measurable gamma globulin.) Later rises were achieved by the administration of large amounts of gamma globulin.

II. Serological Tests

With laboratory techniques used by Kempe, hemagglutination inhibition titer of 1:80 to 1:160 and virus neutralization titer of 1:8 to 1:16 would be expected in normal persons one to two months following vaccination. In this patient low titers following eight weeks of continuous exposure to vaccinia virus (Table 2) indicated inability to produce specific circulating antibody.

Slowly increasing titers were associated with administration of 330 cc. of gamma globulin, 585 cc. of hyperimmune vaccinal gamma globulin, and 1,645 cc. of plasma from recently vaccinated adults.

III. Viral Studies

Inoculation of scrapings of lesions and vesicular fluid on chorio-allantoic membranes of hens' eggs

TABLE 1.—*Results of Serum Protein Studies*

Serum Protein Fractions	Normal for Infants* (Per Cent)	Normal for Adults* (Per Cent)	Patient Dec. 7, 1955 (Per Cent)	Patient Dec. 19, 1955 (Per Cent)	Patient At Death (Per Cent)
Albumin	41.3	52.5	45.0	33.0	38.0
Gamma 1	7.1	4.2	6.0	8.0	7.0
Gamma 2	11.6	12.2	30.0	23.0	16.0
Beta	12.6	14.0	14.0	14.0	7.0
Delta	27.4	17.1	5.0	22.0	32.0

*Sohar, E., et al.: Science 123:461.

TABLE 2.—*Titration Responses at Various Times During Exposure to Vaccinia Virus*

	Dec. 3, 1955	Dec. 8, 1955	Dec. 13, 1955	Dec. 19, 1955	Jan. 7, 1956	Jan. 8, 1956
Hemagglutination inhibition titer	1:10	<1:5	1:5	1:10	1:80	1:40
Complement fixation titer	<1:4	<1:4	<1:4	<1:4	<1:4	<1:4
Virus neutralization titer	0	0	0	1:2	1:8	1:16

resulted in typical vaccinia lesions. Saline solution suspensions of the finely ground membranes agglutinated susceptible chicken red blood cells. This reaction was inhibited by immune vaccinia rabbit serum but not by normal rabbit serum and was considered evidence of the presence of vaccinia virus. Suspension of various tissues obtained at autopsy were also inoculated on the chorio-allantoic membranes of hens' eggs. Typical pock lesions were obtained from suspensions of nerve, lung, stomach, and adrenal tissues.

PATHOLOGIST'S REPORT

Conditions noted at autopsy were as follows: Scattered over the entire body were numerous lesions, some vesicular with umbilicated centers, others with rolled margins and crusted central areas of ulceration. The diameters varied from 1 mm. to 5 or more cm. The dorsal surface of the right hand was completely denuded of epithelium as was most of left hand. Palmar and plantar surfaces were covered by a friable yellow exudate. Petechiae were present over the upper thorax. The pericardial cavity contained 15 cc. of turbid fluid containing several masses of friable yellow material. The epicardium was thickened and a yellow necrotic abscess was present near the coronary sulcus. A 2 mm. friable, yellow vegetation was present on the mitral valve, and two small abscesses were present within the myocardium. Patchy atelectasis was noted in the lungs. An extensive ulceration of the false vocal cords was covered by friable fibrinous exudate. Opposite this area the esophagus showed similar extensive ulceration. The liver was enlarged and studded with small yellow areas of fatty change. Several small ulcerations were observed in the gastrointestinal tract. Two large succulent lymph nodes were present near the bifurcation of the aorta, without other adenopathy. The cranial vault contained a considerable amount of clear fluid and the brain itself appeared small with atrophy of gyri.

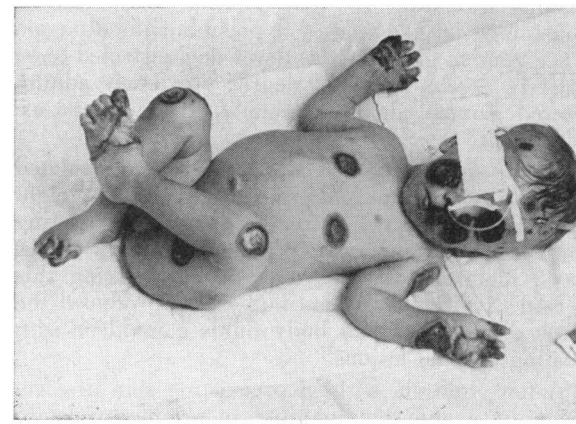

Figure 1.—Photograph six weeks after vaccination showing distribution of lesions.

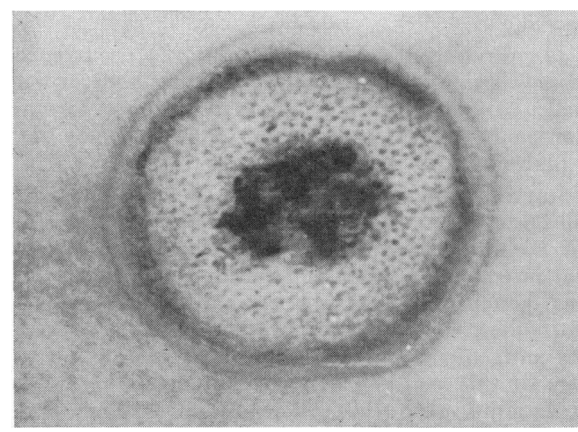

Figure 2.—Close-up view of lesion showing rolled edges and central granulation.

Microscopic examination revealed abscesses in the myocardium and epicardium, with central coagulation necrosis, surrounded by a more chronic inflammatory reaction in which mononuclear phagocytes were prominent. Large clumps of bacteria were

present within the abscess centers. The mitral valve vegetation was composed of granular debris, polymorphonuclear leukocytes and small numbers of bacteria. The thickened underlying valve was infiltrated by multinuclear cells. Ulcerations of larynx and esophagus were morphologically similar to the myocardial abscess cavities. An ulcer of the small intestine showed coagulation necrosis. Skin lesions consisted of vesicles with underlying coagulation necrosis. Other ulcerated skin lesions were covered by coarse necrotic material with relatively few inflammatory cells and no bacteria.

DISCUSSION

The patient in the present case had a rare complication of smallpox vaccination and the conditions were similar to those in previously reported cases of patients with vaccinia gangrenosa and immunologic handicap manifest by deficiency of circulating gamma globulin.[2,7,8,9] The present case must be considered an example of hypogammaglobulinemia since gamma globulin was never demonstrated to be entirely absent. To what degree previously administered gamma globulin contributed cannot be ascertained.

In the normal course of vaccination, inoculated vaccinia virus multiplies locally for six to eight days. During this time viremia may develop, lasting until neutralizing antibodies appear at 12 to 14 days. Metastatic lesions may develop during this period of viremia. As antibodies are produced the virus disappears from body fluids coincident with healing of local lesions.[7]

A few children, without preexisting skin involvement, have apparent inability to produce vaccinia virus neutralizing antibodies either in sufficient quantity or quality. In such children generalized vaccinia with the following characteristics may develop:

(1) Prolonged course of illness; (2) occurrence of new lesions which enlarge, ulcerate and do not heal; (3) demonstrable failure of antibody formation against vaccinia virus and other antigens; (4) a high mortality rate.

Interest in persons deficient in the production of antibodies was aroused by Bruton's report describing a child with pronounced susceptibility to bacterial infections.[3] Absence of serum gamma globulin was demonstrated, as well as inability to produce antibodies, when the child was subjected to numerous antigenic stimuli. Since then increasing awareness of this entity has uncovered many instances of gamma globulin deficiency in children and adults.[4,6,10]

It is of interest that in general, viral infections are usually well tolerated by these patients who have increased susceptibility to bacterial infection. One exception to the general rule is apparent susceptibility to vaccinia virus. Severe necrotizing lesions have been reported with high frequency in patients with this immunologic handicap. On the other hand, many patients with hypogammaglobulinemia have been vaccinated without complications.[3,6]

Most instances of vaccinia gangrenosa have occurred in children with hypogammaglobulinemia, but the disease also occurs in children with normal or elevated gamma globulin levels where antibody production is defective and therefore valueless as a means of defense.[2,8]

Reports of vaccinia gangrenosa are few. Since Ackland's first report in 1893[1] describing a three-months-old infant with this complication, 11 additional cases have been described,[7,9] most of them fatal. Recently, Barbero and co-workers reported the case of a child successfully treated with hyperimmune vaccinal gamma globulin,[2] but the patient differed from the others in that circulating gamma globulin was present in normal quantity.

No satisfactory means of treatment is known. Since antibody production cannot be improved, administration of preformed, normal antibodies is most logical. Hyperimmune gamma globulin and serum from persons recently vaccinated are the only available source of these factors. The quantity administered should be sufficient to produce a measurable neutralizing effect on the vaccinia virus if a fatal outcome is to be prevented. Since neutralizing activity diminishes rapidly within seven to ten days, serum should be administered at frequent intervals. It has been shown that gamma globulin in dosage of 0.1 gm. per kilogram of body weight every 28 days affords protection against bacterial infection in patients with hypogammaglobulinemia.[10]

The second major problem is management of the secondary infection which occurs in the skin lesions. With subsequent systemic invasion, generalized involvement of other organs contributes to the high mortality rate. Hemolytic staphylococcus aureus is the chief offender and successful eradication of it may be difficult because frequently the organism is resistant to antibiotics.

Antibiotic therapy should be first directed to prevention of establishment of the secondary invaders and secondly to eradication of them once they are established. Proper cultural methods with frequent sensitivity studies of isolated organism can guide in choice of drugs.

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Idiopathic Segmental Infarction Of the Omentum

Case Report in a Child

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IDIOPATHIC SEGMENTAL INFARCTION of the greater omentum is one of the rare causes of acute abdominal symptoms. It is even more unusual in children than in adults. Tille[6] collected reports of 26 cases from the literature, only one of which was in a child. Since the review by Tille, five additional cases in children have been reported.[1,3,4,5]

Primary torsion of the omentum with subsequent infarction is an equally rare condition in children—only six cases were mentioned in a recent study by Davis, Mangels and Bolton.[2] Idiopathic segmental infarctions and primary omental torsion with infarction are indistinguishable clinically. They differ only in that definite omental torsion (without evident cause) is the etiological factor in the one group. In children, omental infarction due to any cause has always been confused with acute appendicitis, and operative intervention has generally been prompt.

REPORT OF A CASE

A 9-year-old Caucasian boy was admitted to the Los Angeles County General Hospital on April 21, 1955, because of sharp, persistent pain in the right lower quadrant of the abdomen of one day's duration. Sudden in onset, the pain was initially located in the right lower quadrant and was nonradiating. Anorexia was noted, but there was no nausea, vomiting or change in bowel habit. There was no history of previous similar episodes or of any abdominal injury. The only previous significant illness was mumps.

Upon physical examination the blood pressure was observed to be 100/60 mm. of mercury, the pulse rate 80, the temperature 100° F., and respirations 22 per minute. The patient was well-developed and well nourished. The abdomen was flat; no palpable organs or masses were noted. Peristalsis was present, but hypoactive. There was moderate tenderness with rebound in the right lower quadrant, most pronounced near McBurney's point. No other abnormalities were noted.

The hemoglobin content was 12.0 gm. per 100 cc. of blood. Leukocytes numbered 12,000 per cu. mm. —75 per cent polymorphonuclear cells. Results of urinalysis were within normal limits.

The clinical diagnosis was acute appendicitis. At operation, the abdomen was opened with a McBurney incision and a moderate quantity of serosanguineous fluid was immediately noted. The appendix was observed to be normal. A search was made for a Meckel's diverticulum but none was found. The right lower margin of the greater omentum which lay in the upper portion of the right lower quadrant was a hemorrhagic, infarcted mass 4 x 6 cm. in size. No omental torsion, internal herniation, or any other mechanical factor to account for the omental infarction was noted upon careful inspection. Resection of the infarcted omentum was performed along with appendectomy, and the abdomen was closed without drainage. The postoperative course was uneventful. The pathologic description of the resected specimen was consistent with the gross impression of omental infarction (see Figures 1, 2, 3).

COMMENT

The pathogenesis of idiopathic segmental infarction of the omentum is as obscure as the name implies. The most plausible explanation seems to be that "spontaneous" venous thrombosis occurs and is followed by congestion, inflammatory reaction, necrosis and extravasation of blood. Trauma, temporary torsion, or increased intraabdominal pressure following the ingestion of a heavy meal may be etiologic factors in the initial thrombosis.[6] Attempts have also been made to link obesity with the etiology of omental infarction. The fact that a child's omentum is underdeveloped and often relatively devoid of fat may help to explain the greater rarity of the condition in children than in adults. The most common anatomical site of omental infarction is the right lower margin of the greater omentum.

The clinical symptoms and signs consist of: (1) Pain, either steady or colicky in nature, usually beginning in and remaining in the right lower quadrant of the abdomen; (2) anorexia and nausea usually without vomiting; (3) tenderness, and sometimes rigidity, localized near McBurney's point; and (4) a low grade fever with leukocytosis in most instances.

At operation, dark, bloody peritoneal fluid is found with a gangrenous, edematous, infarcted segment of omentum. Microscopic examination of the infarcted omental tissue shows edema and inflammatory cell infiltration.

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